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2911

SEARCH REQUEST FORM

7-653

Requestor's Name: Russell Travers

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Art Unit: 1614

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

The compound of Claim 1 for an Antiviral use (esp Hepatitis)

1998 JUL 23 AM 11:50

STIC

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Searcher: Mary 4258

Terminal time: 70

Elapsed time: _____

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Vendors

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_____ Dialog

_____ APS

_____ Geninfo

_____ SDC

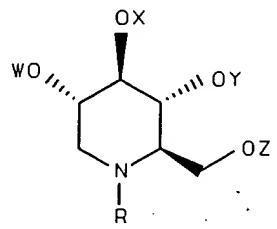
_____ DARC/Questel

_____ Other

PTO-1590 (9-90)

What Is Claimed Is:

1. A method of treating a hepatitis virus infection in a mammal, comprising administering to said mammal a first amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I or a pharmaceutically acceptable salt thereof:



I

wherein:

R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having a chain length of C_1 to C_{20}, and

W, X, Y, and Z are each independently selected from the group consisting of hydrogen, alkanoyl, aroyl, and trifluoroalkanoyl; and

a second amount of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof,

wherein said first and second amounts of said compounds together comprise an anti-hepatitis virus effective amount of said compounds.

2. The method of claim 1, wherein R is a branched or straight chain alkyl having a chain length of C_1 to C_{20}, and W, X, Y, and Z are each hydrogen.

TRAVERS
023401

FILE 'REGISTRY' ENTERED AT 15:48:28 ON 28 JUL 1998
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DICTIONARY FILE UPDATES: 27 JUL 98 HIGHEST RN 208982-86-9

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Stereochemical name changes have been adopted and appear in CN's beginning 6/29/30. See the online news message for details.

```
=> e "1,5-dideoxy-1,5-imino-d-glucitol"/cn

E1            1      1,5-DIDEOXY-1,5-(DODECYLIMINO)-D-MANNITOL/CN
E2            1      1,5-DIDEOXY-1,5-IMINO-D-GALACTITOL/CN
E3            1  --> 1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL/CN
E4            1      1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL FORMATE SALT/CN
E5            1      1,5-DIDEOXY-1,5-IMINO-D-MANNITOL/CN
E6            1      1,5-DIDEOXY-1,5-IMINO-L-FUCITOL/CN
E7            1      1,5-DIDEOXY-1,5-IMINO-N-(5-(METHOXYCARBONYL)PENTYL)-L-
                     FUCITOL/CN
E8            1      1,5-DIDEOXY-CHIRO-INOSADIAMINE-2,4 TETRAACETATE/CN
E9            1      1,5-DIDEOXY-L-ARABINITOL/CN
E10           1      1,5-DIDEUTERIONAPHTHALENE/CN
E11           1      1,5-DIDEUTERIOPENTANE/CN
E12           1      1,5-DIDEUTEROCUBANE/CN

=> s e3

L1            1 "1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL"/CN

=> s e4

L2            1 "1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL FORMATE SALT"/CN

=> s l1 or l2

L3            2 L1 OR L2

=> d ide cbib abs 1-2


L3   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 1998 ACS
RN   154673-53-7  REGISTRY
CN   Formic acid, compd. with [2R-(2.alpha.,3.beta.,4.alpha.,5.beta.)]-2-
     (hydroxymethyl)-3,4,5-piperidinetriol (1:1) (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   3,4,5-Piperidinetriol, 2-(hydroxymethyl)-, [2R-
     (2.alpha.,3.beta.,4.alpha.,5.beta.)]-, formate (salt) (9CI)
OTHER NAMES:
CN   1,5-Dideoxy-1,5-imino-D-glucitol formate salt
FS   STEREOSEARCH
MF   C6 H13 N O4 . C H2 O2
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL
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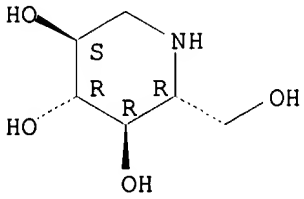
CM 1

CRN 19130-96-2
CMF C6 H13 N O4

Absolute stereochemistry. Rotation (+).



CM 2

CRN 64-18-6
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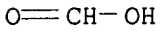
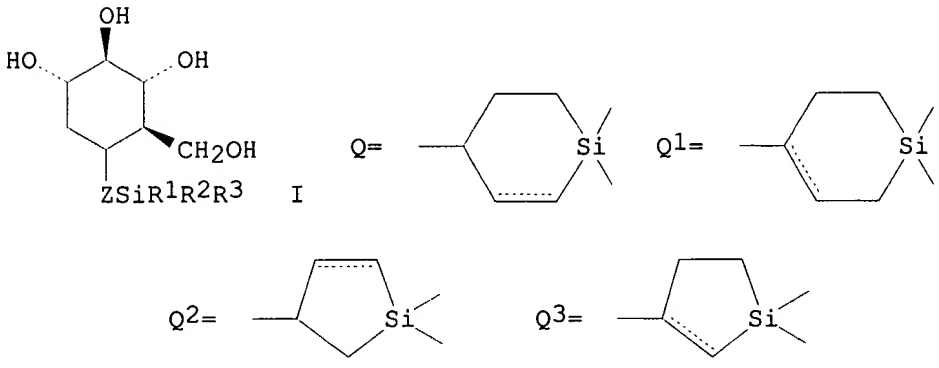


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:57880 Preparation of N-(silylalkyl)deoxynojirimycin derivatives and related compounds for treatment of hyperglycemia. Lesur, Brigitte; Ducep, Jean Bernard; Danzin, Charles (Merrell Dow Pharmaceuticals, Inc., USA). U.S. US 5252587 A 931012, 16 pp. Cont.-in-part of U.S. Ser. No. 691,189, abandoned. (English). CODEN: USXXAM. APPLICATION: US 92-898992 920615. PRIORITY: EP 90-401169 900427; US 91-691189 910425.

GI

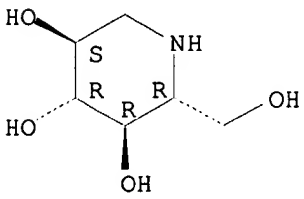


AB The title compds. [I; Z = C1-7 alkylene, (CH2)mCH:CH(CH2)n, (CH2)mC.tplbond.C(CH2)n, (CH2)m(CH:C:CHCH2)n, (CH2)p-phenylene, (CH2)m-cyclopentenylene, (CH2)m-cyclohexenylene, (CH2)pT; T =

trivalent hydrocarbon moiety which, together with the depicted silicon atom, forms the partial structure Q - Q3; the dotted line means a optional double; m = 1-3; n = 0-2; p = 0-4; R1 = C1-7 alkyl or alkoxy, hydroxylated C1-6 alkylene, alkoxylated C1-6 alkylene, C1-6 chloroalkyl; R2, R3 = C1-10 alkyl, Ph(CH2)p optionally having substituents on the ring; provided that when Z = (CH2)pT, one of R1 - R3 is deleted], useful for the treatment of diabetes and infection with retro-virus, particularly AIDS (no data), are prepd. Thus, a soln. of 1,5-dideoxy-1,5-imino-D-glucitol (prepn. given) and (E)-3-trimethylsilyl-2-propen-1-ol in DMF contg. Et3N was heated at 80.degree. for 20 h to give I [ZSiR1R2R3 = (E)-3-(trimethylsilyl)-2-propenyl].

L3 ANSWER 2 OF 2 REGISTRY COPYRIGHT 1998 ACS
RN 19130-96-2 REGISTRY
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-, [2R-(2.alpha.,3.beta.,4.alpha.,5.beta.)]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glucopyranose, 5-amino-1,5-dideoxy-, D- (8CI)
OTHER NAMES:
CN **1,5-Dideoxy-1,5-imino-D-glucitol**
CN 1-Deoxynojirimicin
CN 1-Deoxynojirimycin
CN 5-Amino-1,5-dideoxy-D-glucopyranose
CN BAY-h 5595
CN D-Glucitol, 1,5-dideoxy-1,5-imino-
CN Deoxynojirimycin
CN Moranolin
CN Moranoline
CN Nojirimycin, 1-deoxy-
FS STEREOSEARCH
DR 70956-02-4
MF C6 H13 N O4
CI COM
LC STN Files: AGRICOLA, AIDSLINE, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CJACS, CSCHEM, DDFU, DRUGU, EMBASE, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PHAR, PNI, PROMT, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



369 REFERENCES IN FILE CA (1967 TO DATE)
34 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
369 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:52086 .alpha.-Homonojirimycin from Hyacinthus orientalis L.. Kite, Geoffrey C.; Sellwood, Chloe; Wilkin, Paul; Simmonds, Monique S. J. (The Jodrell Laboratory, Royal Botanic Gardens, Surrey, TW9 3AB, UK). Biochem. Syst. Ecol., 26(3), 357-359

(English) 1998. CODEN: BSECBU. ISSN: 0305-1978. Publisher: Elsevier Science Ltd..

AB .alpha.-Homonojirimycin was isolated together with some related compds. from the leaves of 4 subspecies of H. orientalis, but was not found in other Hyacynthaceae. The chemotax. significance of this finding is discussed.

REFERENCE 2: 129:23913 Cloning, nucleotide sequence, and expression of the Clostridium thermocellum cellodextrin phosphorylase gene and its application to synthesis of cellulase inhibitors. Kawaguchi, Takashi; Ikeuchi, Yasuo; Tsutsumi, Noriko; Kan, Akihiko; Sumitani, Jun-Ichi; Arai, Motoo (Department of Applied Biological Chemistry, College of Agriculture, Osaka Prefecture University, Osaka, 599-8531, Japan). J. Ferment. Bioeng., 85(2), 144-149 (English) 1998. CODEN: JFBIEX. ISSN: 0922-338X. Publisher: Society for Fermentation and Bioengineering, Japan.

AB The cellodextrin phosphorylase (CDP) gene of Clostridium thermocellum was cloned and sequenced. The nucleotide sequence of the insert of a pos. clone contained an open reading frame of 2940 bp encoding a polypeptide of 980 amino acid residues with a calcd. mol. mass of 111,182 Da. Escherichia coli cells harboring the plasmid for expression produced CDP protein accounting for 30% of the total cellular proteins with an activity of 59.9 units/mL culture, which corresponded to 0.93 mg/mL culture. The expressed CDP could be used to synthesize cellulase inhibitors as cellooligosaccharide analogs using glucose-1-phosphate as a glucose donor and 4-O-.beta.-D-glucopyranosyl-1-deoxynojirimycin or 6-O-.beta.-cellobiosyl-1-deoxynojirimycin as an acceptor.

REFERENCE 3: 129:8587 Method and compositions for disrupting the epithelial barrier function. Elias, Peter M.; Feingold, Kenneth R.; Holleran, Walter M.; Thornfeldt, Carl R. (Regents of the University of California, USA; Cellegy Pharmaceuticals, Inc.). PCT Int. Appl. WO 9817253 A1 980430, 62 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 97-US19343 971022. PRIORITY: US 96-733712 961023.

AB Epithelial barrier function is disrupted in a host in need of topical administration of a physiol. active substance by applying to the epithelium a barrier-disrupting amt. of .gtoreq.1 agent selected from (1) inhibitors of synthesis of ceramides, acylceramides, glucosylceramides, sphingomyelins, fatty acids, or cholesterol; (2) degrdn. enzymes for ceramides, acylceramides, glucosylceramides, or sphingomyelins; (3) inhibitors of degrdn. of phospholipids, glycosphingolipids, glucosylceramides, acylceramides, or sphingomyelins; and (4) inhibitors and stimulators of metabolic enzymes of free fatty acids, ceramides, and cholesterol. Thus, a combination of 5-tetradecyloxy-2-furancarboxylic acid (an inhibitor of acetyl-CoA carboxylase which is the rate-limiting enzyme in free fatty acid synthesis) and .beta.-chloroalanine (an inhibitor of serine palmitoyltransferase, the rate-limiting enzyme in ceramide synthesis) increased delivery of lidocaine through mouse stratum corneum by 8-fold in vivo and increased transepidermal water loss. Thus, a combination of 5-tetradecyloxy-2-furancarboxylic acid (an inhibitor of acetyl-CoA carboxylase which is the rate-limiting enzyme in free fatty acid synthesis) and .beta.-chloroalanine (an

inhibitor of serine palmitoyltransferase, the rate-limiting enzyme in ceramide synthesis) increased delivery of lidocaine through mouse stratum corneum by 8-fold in vivo and increased transepidermal water loss.

REFERENCE 4: 129:4789 Enzymic synthesis of 6-O-.alpha.-D-galactopyranosyl-1-deoxynojirimycin using .alpha.-galactosidase from green coffee beans. Paek, Nam Soo; Kang, Dae Jung; Lee, Hong Sub; Lee, Jung Joon; Choi, Yong Jin; Kim, Tae Han; Kim, Kee Won (Research Laboratories, IlDong Pharmaceutical Co., Kyongki-do, 60-1, S. Korea). Biosci., Biotechnol., Biochem., 62(3), 588-589 (English) 1998. CODEN: BBBIEJ. ISSN: 0916-8451. Publisher: Japan Society for Bioscience, Biotechnology, and Agrochemistry.

AB A transgalactosylation reaction from p-nitrophenyl-.alpha.-D-galactopyranoside to 1-deoxynojirimycin was done using .alpha.-galactosidase [EC 3.2.1.22] from green coffee beans. The enzyme formed 6-O-.alpha.-D-galactopyranosyl-1-deoxynojirimycin as the major product.

REFERENCE 5: 129:2068 A glycosidase antibody elicited against a chair-like transition state analog by in vitro immunization. Yu, Jaehoon; Choi, So Young; Moon, Kyung-Duk; Chung, Hyun-Ho; Youn, Hyun Joo; Jeong, Sunjoo; Park, Hokoon; Schultz, Peter G. (Division Applied Science, Korea Institute Science Technology, Seoul, 131-791, S. Korea). Proc. Natl. Acad. Sci. U. S. A., 95(6), 2880-2884 (English) 1998. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

AB Antibodies were generated against the pos. charged chair-like glycosidase inhibitor nojirimycin by in vitro immunization. A no. of catalytic antibodies were isolated, one of which catalyzes the hydrolysis of p-nitrophenyl .beta.-D-glucopyranoside with a rate enhancement (kcat/kuncat) of 105 M over the HOAC-catalyzed reaction. The antibody discriminates modifications in the pyranoside ring of substrate at the C2, C4, and the anomeric positions. The pH dependence of the reaction and chem. modification studies suggest the presence of an active-site Asp or Glu residue that may function as a general acid. This study further defines those requirements necessary to generate antibodies that efficiently cleave glycosidic bonds.

REFERENCE 6: 128:305941 Diagnosis of spongiform encephalopathy. Collinge, John (Imperial College of Science, Technology and Medicine, UK; Collinge, John). PCT Int. Appl. WO 9816834 A1 980423, 50 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 97-GB2843 971015. PRIORITY: GB 96-21469 961015; GB 96-21885 961021.

AB The present invention relates to a method for typing a sample of a prion or spongiform encephalopathy disease, a kit suitable for use in such a typing method, a method for identifying infection in an animal and/or tissue of bovine spongiform encephalopathy (BSE), a method for assessing and/or predicting the susceptibility of an animal to BSE, a kit for use in such an assessment and/or prediction method, a method for the treatment of a prion disease, compds. suitable for such a method, use of such compds. and pharmaceutical agents comprising such compds.

REFERENCE 7: 128:280836 Nitrogen-Containing Furanose and Pyranose Analogs from Hyacinthus orientalis. Asano, Naoki; Kato, Atsushi; Miyauchi, Miwa; Kizu, Haruhisa; Kameda, Yukihiko; Watson, Alison A.; Nash, Robert J.; Fleet, George W. J. (Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa, 920-11, Japan). J. Nat. Prod., 61(5), 625-628 (English) 1998. CODEN: JNPRDF. ISSN: 0163-3864. Publisher: American Chemical Society.

AB Aq. methanol exts. from the bulbs of Hyacinthus orientalis were subjected to various ion-exchange column chromatog. steps to give 2(R),5(R)-bis(hydroxymethyl)-3(R),4(R)-dihydroxypyrrolidine (DMDP) (1), 2,5-dideoxy-2,5-imino-DL-glycero-D-manno-heptitol (homoDMDP) (2), 2,5-imino-2,5,6-trideoxy-D-manno-heptitol (6-deoxy-homoDMDP) (3), 2,5-imino-2,5,6-trideoxy-D-gulo-heptitol (4), 1-deoxynojirimycin (5), 1-deoxymannojirimycin (6), .alpha.-homonojirimycin (7), .beta.-homonojirimycin (8), .alpha.-homomannojirimycin (9), .beta.-homomannojirimycin (10), and 7-O-.beta.-D-glucopyranosyl-.alpha.-homonojirimycin (MDL 25,637) (11). The structures of the new natural products 3 and 4 were detd. by spectroscopic anal., including extensive 1D and 2D NMR studies. Compd. 2 was a potent inhibitor of bacterial .beta.-glucosidase, mammalian .beta.-galactosidases, and mammalian trehalases, while 3 was a potent inhibitor of rice .alpha.-glucosidase and rat intestinal maltase. Compd. 4 was obsd. to be a good inhibitor of .alpha.-L-fucosidase.

REFERENCE 8: 128:270798 Improved synthesis of 1-deoxynojirimycin and facile synthesis of its stereoisomers from (S)-pyroglutamic acid derivative. Ikota, Nobuo; Hirano, Jun-ichi; Gamage, Ranjith; Nakagawa, Hidehiko; Hama-Inaba, Hiroko (National Inst. Radiological Sci., Chiba, 263, Japan). Heterocycles, 46, 637-644 (English) 1997. CODEN: HTCYAM. ISSN: 0385-5414. Publisher: Japan Institute of Heterocyclic Chemistry.

AB Improved synthesis of 1-deoxynojirimycin from (E)-.alpha.,.beta.-unsatd. ester and facile synthesis of 1-deoxyazasugars where both substrates prepd. from (S)-pyroglutamic acid were described.

REFERENCE 9: 128:241136 Enzymic properties of the cysteinesulfinic acid derivative of the catalytic-base mutant Glu400.fwdarw.Cys of glucoamylase from Aspergillus awamori. Fierobe, Henri-Pierre; Clarke, Anthony J.; Tull, Dedreia; Svensson, Birte (Department of Chemistry, Carlsberg Laboratory, Copenhagen Valby, DK-2500, Den.). Biochemistry, 37(11), 3753-3759 (English) 1998. CODEN: BICHAW. ISSN: 0006-2960. Publisher: American Chemical Society.

AB The pKa of the catalytic base was lowered and its distance to the general acid catalyst, Glu-179, was increased in the glucoamylase from Aspergillus awamori by replacing the catalytic base Glu-400 with cysteine followed by oxidn. to cysteinesulfinic acid. 1H NMR spectroscopy demonstrated that the oxidized mutant Glu-400.fwdarw.Cys-SO2H glucoamylase, like the wild-type, catalyzed hydrolysis with inversion of the anomeric configuration of the product. Relative to the catalytic base mutant Glu-400.fwdarw.Cys, the Cys-400-SO2H glucoamylase had 700 times higher kcat toward maltose, while Km was unchanged. Compared to wild-type glucoamylase, the Cys-400-SO2H deriv. had kcat values of 150-190% and 85-320% on malto- and isomaltooligosaccharides, resp., while Km values were similar to those of wild-type with the 2 disaccharides and 3.5-5.5- and 1.8-2.5-fold higher for the longer malto- and isomaltooligosaccharides substrates, resp. The pH-activity dependence at satg. concn. of maltose indicated that the pKa of the catalytic base Cys-400-SO2H was about 0.5 pH unit lower than that of

wild-type Glu-400. The Ki of Cys-400-SO2H glucoamylase for the pseudotetrasaccharide and potent inhibitor acarbose increased >104-fold, but Ki values of the mono- and disaccharide analogs 1-deoxynojirimycin and .beta.-O-methylacarviosinide were unchanged, suggesting perturbation at binding subsites beyond the catalytic center. A distinct property of Cys-400-SO2H glucoamylase was the catalysis of the condensation of .beta.-D-glucopyranosyl fluoride and subsequent hydrolysis of the product to .beta.-glucose, under conditions where this was not detected for the wild-type enzyme.

REFERENCE 10: 128:239283 Antihyperglycemic Effects of N-Containing Sugars from Xanthocercis zambesiaca, Morus bombycis, Aglaonema treubii, and Castanospermum australe in Streptozotocin-Diabetic Mice. Nojima, Hiroshi; Kimura, Ikuko; Chen, Fu-jun; Sugihara, Yoshitaka; Haruno, Motoko; Kato, Atsushi; Asano, Naoki (Department of Chemical Pharmacology Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Toyama, 930-01, Japan). J. Nat. Prod., 61(3), 397-400 (English) 1998. CODEN: JNPRDF. ISSN: 0163-3864. Publisher: American Chemical Society.

AB The aq. MeOH ext. of the leaves and root of Xanthocercis zambesiaca (Leguminosae) and eight structurally related nitrogen-contg. sugars, fagomine (1), 4-O-.beta.-D-glucopyranosylfagomine (2), 3-O-.beta.-D-glucopyranosylfagomine (3), 3-epifagomine (4), 2,5-dideoxy-2,5-imino-D-mannitol (5), castanospermine (6), .alpha.-homonojirimycin (7), and 1-deoxynojirimycin (8) were evaluated for antihyperglycemic effects in streptozotocin (STZ)-diabetic mice. The insulin-releasing effects of 1 were also investigated. The blood glucose level fell after i.p. injection of the ext. (50 mg/kg). Compds. 1, 2, 5, and 6 reduced the blood glucose level after i.p. injection of 150 .mu.mol/kg. Compd. 1 increased plasma insulin level in STZ-diabetic mice and potentiated the 8.3-mM glucose-induced insulin release from the rat isolated-perfused pancreas. The 1-induced potentiation of insulin release may partly contribute to antihyperglycemic action.

=> fil caplus,.biotech,uspatful;s (l1 or l2 or dideoxy(5a)imino(3a)glucitol) and hepatit?

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L5	1	FILE BIOSIS
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TOTAL FOR ALL FILES
L9 15 (L1 OR L2 OR DIDEOXY(5A) IMINO(3A) GLUCITOL) AND HEPATIT?

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PROCESSING COMPLETED FOR L9
L10 12 DUP REM L9 (3 DUPLICATES REMOVED)

=> d 1-12 cbib abs

L10 ANSWER 1 OF 12 MEDLINE
1998244636 Document Number: 98244636. Treatment of chronic hepadnavirus infection in a woodchuck animal model with an inhibitor of protein folding and trafficking. Block T M; Lu X; Mehta A S; Blumberg B S; Tennant B; Ebling M; Korba B; Lansky D M; Jacob G S; Dwek R A. (Viral Hepatitis Group, Kimmel Cancer Center, Jefferson Medical College, Philadelphia, Pennsylvania 19107, USA.)NATURE MEDICINE, (1998 May) 4 (5) 610-4. Journal code: CG5. ISSN: 1078-8956. Pub. country: United States. Language: English.
AB A novel strategy for anti-viral intervention of **hepatitis** B virus (HBV) through the disruption of the proper folding and transport of the hepadnavirus glycoproteins is described. Laboratory reared woodchucks chronically infected with woodchuck **hepatitis** virus (WHV) were treated with N-nonyl-deoxynojirimycin (N-nonyl-DNJ), an inhibitor of the endoplasmic reticulum (ER) alpha-glucosidases. The woodchucks experienced significant dose dependent decreases in enveloped WHV, resulting in undetectable amounts in some cases. The reduction in viremia correlated with the levels of hyperglucosylated glycan in the serum of treated animals. This correlation supports the mechanism of action associated with the drug and highlights the extreme sensitivity of the virus to this type of glycan inhibitor. At N-nonyl-DNJ concentrations that prevented WHV secretion, the glycosylation of most serum glycoproteins appeared unaffected, suggesting great selectivity for this class of therapeutics. Indeed, this may account for the low toxicity of the compound over the treatment period. We provide the first evidence that glucosidase inhibitors can be used in vivo to alter specific steps in the N-linked glycosylation pathway and that this inhibition has anti-viral effects.

L10 ANSWER 2 OF 12 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
1998223378 EMBASE .alpha.-Glucosidase inhibitors as potential broad based anti-viral agnets. Mehta A.; Zitzmann N.; Rudd P.M.; Block T.M.; Dwek R.A.. R.A. Dwek, Glycobiology Institute, Department of Biochemistry, Oxford University, Oxford OX1 3QU, United Kingdom.
FEBS Letters 430/1-2 (17-22) 23 Jun 1998.
Refs: 30.
ISSN: 0014-5793. CODEN: FEBLAL.
Publisher Ident.: S 0014-5793(98)00525-0. Pub. Country: Netherlands.
Language: English. Summary Language: English.
AB N-linked oligosaccharides play many roles in the fate and functions of glycoproteins. One function is to assist in the folding of proteins by mediating interactions of the lectin-like chaperone proteins calnexin and calreticulin with nascent glycoproteins. These interactions can be prevented by inhibitors of the .alpha.-glucosidases and this causes some proteins to be misfolded and retained within the endoplasmic reticulum. In human immunodeficiency virus (HIV) and **hepatitis** B virus (HBV) the misfolding of key viral envelope glycoproteins interferes with

the viral life cycle. It has been demonstrated in an animal model of chronic HBV that glucosidase inhibitors can alter glycosylation and have anti-viral activity. As the mechanism of action of .alpha.-glucosidase inhibitors is the induction of misfolded or otherwise defective viral glycoproteins, such inhibitors may be useful therapeutics for many viruses, especially those which bud from the endoplasmic reticulum (where protein folding takes place). For example bovine viral diarrhea virus, a pestivirus akin to **hepatitis** C virus, is also extremely sensitive to glucosidase inhibition.

L10 ANSWER 3 OF 12 MEDLINE

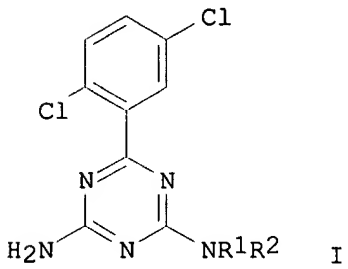
97203145 Document Number: 97203145. **Hepatitis** B virus (HBV) envelope glycoproteins vary drastically in their sensitivity to glycan processing: evidence that alteration of a single N-linked glycosylation site can regulate HBV secretion. Mehta A; Lu X; Block T M; Blumberg B S; Dwek R A. (The Glycobiology Institute, Department of Biochemistry, Oxford University, United Kingdom.)PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Mar 4) 94 (5) 1822-7. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The role of N-linked glycosylation and glycan trimming in the function of glycoproteins remains a central question in biology. **Hepatitis** B virus specifies three glycoproteins (L, M, and S) that are derived from alternate translation of the same ORF. All three glycoproteins contain a common N-glycosylation site in the S domain while M possesses an additional N-glycosylation site at its amino terminus. In the presence of N-butyl-deoxnojirimycin (an inhibitor of alpha-glucosidase) virions and the M protein are surprisingly retained. Preliminary evidence suggests that the retained M protein is hyperglucosylated and localized to lysosomal vesicles. In contrast, the S and L proteins are secreted, and their glycosylation state is unaffected by the presence of the inhibitor. Site-directed mutagenesis provides evidence that virion secretion requires the glycosylation sequon in the pre-S2 domain of M. This highlights the potential role of the M protein oligosaccharide as a therapeutic target.

L10 ANSWER 4 OF 12 CAPLUS COPYRIGHT 1998 ACS

1996:385934 Document No. 125:41767 Synthesis and formulation of triazine derivatives as **hepatitis** remedies. Ueda, Fusao; Ozaki, Takayuki; Nakamura, Ken-ichi (Nippon Shinyaku Co., Ltd., Japan). PCT Int. Appl. WO 9604914 A1 960222, 56 pp. DESIGNATED STATES: W: AU, BR, CA, CN, FI, HU, JP, KR, MX, NO, NZ, RU, UA, US, VN; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 95-JP1577 950808. PRIORITY: JP 94-185810 940808.

GI



I

AB A medicine useful as a **hepatitis** remedy is claimed which contains as the active ingredient a triazine deriv. represented by general formula (I), a solvate thereof, or a salt thereof, wherein R1 and R2 represent each independently hydrogen or (un)substituted alkyl, aralkyl or alkenyl, or NR1R2 represents a cyclic amino group which may bear, in addn. to the pertinent nitrogen atom, nitrogen, oxygen or sulfur as the ring atom and may be substituted, provided the case where NR1R2 represents NH2 is excluded. Studies in mouse and rat models of **hepatitis** indicate the remedial efficacy of various I.

L10 ANSWER 5 OF 12 MEDLINE

96183873 Document Number: 96183873. Protease-induced infectivity of **hepatitis** B virus for a human hepatoblastoma cell line. Lu X; Block T M; Gerlich W H. (Institute of Medical Virology, Justus-Liebig-University, Giessen, Germany.)JOURNAL OF VIROLOGY, (1996 Apr) 70 (4) 2277-85. Journal code: KCV. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The human hepatoblastoma cell line HepG2 produces and secretes **hepatitis** B virus (HBV) after transfection of cloned HBV DNA. Intact virions do not infect these cells, although they attach to the surface of the HepG2 cell through binding sites in the pre-S1 domain. Entry of enveloped virions into the cell often requires proteolytic cleavage of a viral surface protein that is involved in fusion between the cell membrane and the viral envelope. Recently, we observed pre-S-independent, nonspecific binding between **hepatitis** B surface (HBs) particles and HepG2 cells after treatment of HBs antigen particles with V8 protease, which cleaves next to a putative fusion sequence. Chymotrypsin removed this fusion sequence and did not induce binding. In this study, we postulate that lack of a suitable fusion-activating protease was the reason why the HepG2 cells were not susceptible to HBV. To test this hypothesis, virions were partially purified from the plasma of HBV carriers and treated with either staphylococcal V8 or porcine chymotrypsin protease. Protease-digested virus lost reactivity with pre-S2-specific antibody but remained morphologically intact as determined by electron microscopy. After separation from the proteases, virions were incubated with HepG2 cells at pH 5.5. Cultures inoculated with either intact or chymotrypsin-digested virus did not contain detectable levels of intracellular HBV DNA at any time following infection. However, in cultures inoculated with V8-digested virions, HBV-specific products, including covalently closed circular DNA, viral RNA, and viral pre-S2 antigen, could be detected in a time-dependent manner following infection. Immunofluorescence analysis revealed that 10 to 30% of the infected HepG2 cells produced HBV antigen. Persistent secretion of virus by the infected HepG2 cells lasted at least 14 days and was maintained during several reseeding steps. The results show that V8-digested HBV can productively infect tissue cultures of HepG2 cells. It is suggested that proteolysis-dependent exposure of a fusion domain within the envelope protein of HBV is necessary during natural infection.

L10 ANSWER 6 OF 12 CAPLUS COPYRIGHT 1998 ACS DUPLICATE 1

1996:676601 Document No. 126:166108 Copper(II) interactions with an experimental antiviral agent, 1-deoxynojirimycin, and oxygen activation by resulting complexes. Jezowska-Bojczuk, Malgorzata; Bal, Wojciech; Kasprzak, Kazimierz S. (Faculty of Chemistry, University of Wroclaw, Wroclaw, 50-383, Pol.). J. Inorg. Biochem.,

64(4), 231-246 (English) 1996. CODEN: JIBIDJ. ISSN: 0162-0134. Publisher: Elsevier.

AB 1-Deoxynojirimycin (DNJ), a 5-imino analog of 1-deoxyglucose, is a potent inhibitor of .alpha.-glucosidase I. DNJ and its derivs. have been considered as exptl. drugs against human HIV-1 and **hepatitis** B viruses. Since amino and imino ligands have a high affinity for copper, it seems possible that biol. activity of DNJ may be, at least in part, modulated by tissue copper. To test this possibility, potentiometric and spectroscopic studies of the complexation of DNJ by cupric ions were performed to obtain thermodn. and structural background for further pharmacol. investigations. The effect of histidine, a major tissue copper carrier, on coordination equil. was also studied. Results indicate that DNJ and Cu(II) form two stable complexes at physiol. pH, CuH-1(DNJ)2+ and CuH-2(DNJ)2, involving Cu(II) chelation by the N-5 and O-6 donor atoms. In the presence of histidine, ternary complexes are also formed, of which the CuDNJHis+ species is stable in the physiol. pH range. Binary Cu(II)-DNJ complexes are extremely effective mediators of in vitro oxidn. of the guanine moiety in both 2'-deoxyguanosine (dG) and DNA to 8-oxoguanine (8-oxo-dG) and DNA double strand scission by ambient O2 or H2O2. This mediation is suppressed by histidine in dG, but not in DNA. The results suggest that tissue Cu(II) may greatly enhance nonspecific cytotoxic effects of systemically administered DNJ through oxidative damage mechanisms, and therefore the prospective use of DNJ for therapeutic purposes must be developed with caution. However, the expected high genotoxic potential of synthetic Cu(II)-DNJ complexes may be used against viruses by targeted delivery of these complexes to the infected cells.

L10 ANSWER 7 OF 12 CAPLUS COPYRIGHT 1998 ACS

1995:785110 Document No. 123:160827 Use of N-alkyl derivatives of 1,5-**dideoxy**-1,5-**imino**-D-**glucitol** for the treatment of **hepatitis** B virus infections. Block, Timothy M.; Blumberg, Baruch S.; Dwek, Raymond A. (G.D. Searle and Co., USA; Monsanto Co.). PCT Int. Appl. WO 9519172 A1 950720, 29 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 94-US14548 941223. PRIORITY: US 94-181519 940113.

AB A method is disclosed for the treatment of **hepatitis** B virus (HBV) infections, which comprises administering to the infected host an N-alkyl deriv. of 1,5-dideoxy-1,5-imido-D-glucitol in which the alkyl group contains from 3 to 6 carbon atoms. In examples, N-butyl-1,5-**dideoxy**-1,5-**imino**-D-**glucitol** was shown to suppress the secretion of HBV particles and to cause intracellular retention of HBV DNA in both stably transfected HepG 2.2.15 cells and HBV-infected HepG 2 cells.

L10 ANSWER 8 OF 12 MEDLINE

96074541 Document Number: 96074541. Evidence that N-linked glycosylation is necessary for **hepatitis** B virus secretion. Lu X; Mehta A; Dwek R; Butters T; Block T. (Viral Hepatitis Group, Jefferson Cancer Institute, Jefferson Medical College, Philadelphia, Pennsylvania 19107-6799, USA.)VIROLOGY, (1995 Nov 10) 213 (2) 660-5. Journal code: XEA. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Human **hepatitis** B virus (HBV) envelopes contain three

distinct glycoproteins called L, M, and S HBsAg. Each is posttranslationally modified to contain N-linked oligosaccharides. N-linked oligosaccharides, after attachment to a polypeptide backbone, are processed by enzymes within the endoplasmic reticulum (ER). There is uncertainty about what role, if any, these N glycans and their modification in the ER play in the function of the HBV envelope proteins. By treating hepatoblastoma cultures which secrete HBV (HepG 2.2.15 cells) with inhibitors of different steps of the glycosylation and glycan modifying pathway, we provide evidence that glycosylation and the first step in the processing pathway are necessary for virion, but not subviral particle, secretion. That is, using a highly sensitive immunoprecipitation/polymerase chain reaction system, enveloped HBV could not be detected in the medium of HepG2.2.15 cells incubated with tunicamycin. However, HBV subviral particle secretion was not prevented by tunicamycin. Moreover, inhibitors of alpha-glucosidase I (the first step in the glycan processing pathway) also prevented virion secretion. Inhibitors of mannose trimming (a later step) and glycolipid synthesis, did not prevent virion secretion, defining the limits of the glycosylation requirements in secretion. These results demonstrate a requirement for N-glycosylation and glucosidase processing in the secretion of virions and further distinguish between the requirements for virion and subviral particle secretion.

L10 ANSWER 9 OF 12 MEDLINE
94181567 Document Number: 94181567. Secretion of human **hepatitis** B virus is inhibited by the imino sugar N-butyldeoxynojirimycin. Block T M; Lu X; Platt F M; Foster G R; Gerlich W H; Blumberg B S; Dwek R A. (Jefferson Cancer Institute, Jefferson Medical College, Philadelphia, PA 19107.)PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Mar 15) 91 (6) 2235-9. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The imino sugar N-butyldeoxynojirimycin (NBDNJ) is a potent inhibitor of the oligosaccharide-trimming enzyme alpha-glucosidase I. **Hepatitis** B virus (HBV) contains three surface proteins (HBs proteins) of different sizes that are singly or doubly N-glycosylated and are essential for the formation of infectious virus. Therefore, the replication and secretion of HBV in the human hepatoma cell line HepG2 were studied in the presence of NBDNJ. In the stably HBV-transfected HepG 2.2.15 cells and in HBV-infected HepG2 cells, NBDNJ suppressed secretion of HBV particles and caused intracellular retention of HBV DNA. The secretion of subviral particles was less affected. These data suggest that inhibitors of oligosaccharide trimming may be useful for antiviral therapy of **hepatitis** B and for the study of the intracellular transport of the viral glycoproteins.

L10 ANSWER 10 OF 12 USPATFULL
90:54601 N-substituted derivatives of 1-desoxynojirimycin and 1-desoxymannonojirimycin and pharmaceutical use.
Boshagen, Horst, Haan, Germany, Federal Republic of
Junge, Bodo, Wuppertal, Germany, Federal Republic of
Paessens, Arnold, Haan, Germany, Federal Republic of
Schuller, Matthias, Wuppertal, Germany, Federal Republic of
Bayer Aktiengesellschaft, Leverkusen, Germany, Federal Republic of (non-U.S. corporation)
US 4940705 900710
APPLICATION: US 88-262902 881026 (7)
PRIORITY: DE 87-3736771 871030
DE 88-3814549 880429

DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB N-substituted derivatives of 1-desoxynojirimycin and 1-desoxymannojirimycin of the formula ##STR1## in which one of R and R' are hydroxyl and the other is hydrogen

n is a number from 1 to 6

R.sup.1 is hydrogen, alkyl or benzyl and

R.sup.2 is alkyl which is optionally substituted by an optionally substituted aryl or by pyridyl, thienyl, furyl, pyrimidyl, pyrazinyl or quinolyl or R.sub.1 is cycloalkyl or R.sup.2 is optionally substituted by aryl or R.sup.2 is a saturated bridged heterocycle or R.sup.1 and R.sup.2 together can form a heterocyclic ring which is optionally substituted. These compounds are useful in the treatment of and prophylaxis of viral infections.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 11 OF 12 MEDLINE
88318020 Document Number: 88318020. Studies on the effect of 1-deoxynojirimycin on the release of albumin, sialyltransferase and alpha 1 acid glycoprotein from liver slices from normal and inflamed rats. Jamieson J C. (Department of Chemistry, University of Manitoba, Winnipeg, Canada.)LIFE SCIENCES, (1988) 43 (8) 691-7. Journal code: L62. ISSN: 0024-3205. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Liver slices from control and 24hr inflamed rats were incubated for up to 20hr with 5mM 1-deoxynojirimycin (DN), an inhibitor of the processing glucosidases. The amounts of albumin and alpha 1-acid glycoprotein (AGP) and the activities of sialyltransferase were determined in liver and medium. The presence of DN significantly inhibited the release of AGP and sialyltransferase. The inhibitory effect of DN was most pronounced with slices from inflamed rats. Secretion of albumin was not inhibited. Incorporation studies with labelled leucine and mannose showed that the inhibitor did not significantly affect protein synthesis, but it did inhibit mannose incorporation into AGP and sialyltransferase. The results show that DN inhibits the secretion of acute phase AGP and sialyltransferase in liver slices and further suggests that sialyltransferase is a glycoprotein.

L10 ANSWER 12 OF 12 MEDLINE
86059476 Document Number: 86059476. The effects of processing inhibitors of N-linked oligosaccharides on the intracellular migration of glycoprotein E2 of mouse **hepatitis** virus and the maturation of coronavirus particles. Repp R; Tamura T; Boschek C B; Wege H; Schwarz R T; Niemann H. JOURNAL OF BIOLOGICAL CHEMISTRY, (1985 Dec 15) 260 (29) 15873-9. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB We have studied the effects of tunicamycin and inhibitors of the processing of N-linked glycans including N-methyl-1-deoxynojirimycin, castanospermine, mannodeoxynojirimycin, and swainsonine on the transport of glycoprotein E2 and the intracellular maturation of the coronavirus mouse **hepatitis** virus A59. Indirect immunofluorescence staining with monoclonal antibodies revealed that glycoprotein E2 exhibits different antigenic properties depending on the presence and on the structure of the N-linked oligosaccharides and that efficient transport of

glycoprotein E2 to the plasma membrane requires the removal of glucose residues. In the presence of tunicamycin in the nonglycosylated E2 apoprotein was synthesized in normal amounts and readily acylated throughout the infectious cycle. This E2-species could not be detected on the surface of mouse **hepatitis** virus A59-infected cells with indirect immunofluorescence staining or lactoperoxidase labeling. N-Methyl-1-deoxynojirimycin and castanospermine, both of which selectively inhibited the processing glucosidases, caused a drop in virion formation by two log steps and a drastic delay in the surface expression of glycoprotein E2. The E2 species synthesized under such conditions was acylated but accumulated intracellularly in a compartment distinct from the Golgi. Concomitantly, synthesis of the matrix glycoprotein E1 of mouse **hepatitis** virus A59 was drastically impaired. Mannodeoxynojirimycin and swainsonine, which block later stages of the processing pathway, had less or no effect on the transport of glycoprotein E2 and the formation of virus particles.

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DICTIONARY FILE UPDATES: 27 JUL 98 HIGHEST RN 208982-86-9

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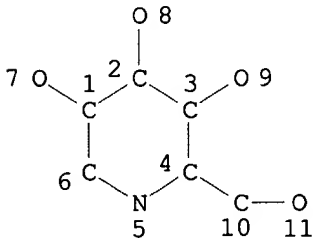

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DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE
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FILE 'MEDLINE' ENTERED AT 15:53:49 ON 28 JUL 1998

FILE 'EMBASE' ENTERED AT 15:53:49 ON 28 JUL 1998

FILE 'USPATFULL' ENTERED AT 15:53:49 ON 28 JUL 1998

L14 8 FILE CAPLUS
L15 3 FILE BIOSIS
L16 8 FILE MEDLINE
L17 4 FILE EMBASE
L18 1 FILE USPATFULL

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L2 1 S E4
L3 2 S L1 OR L2

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L5 1 FILE BIOSIS
L6 8 FILE MEDLINE
L7 2 FILE EMBASE
L8 1 FILE USPATFULL
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L10 12 DUP REM L9 (3 DUPLICATES REMOVED)

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L13 2141 S L11 FUL

FILE 'CAPLUS, BIOSIS, MEDLINE, EMBASE, USPATFULL' ENTERED AT 15:53:49 ON 28 JUL 1998

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L14             8 FILE CAPLUS
L15             3 FILE BIOSIS
L16             8 FILE MEDLINE
L17             4 FILE EMBASE
L18             1 FILE USPATFULL
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L19            24 S L13 AND HEPATITIS

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L20             5 FILE CAPLUS
L21             2 FILE BIOSIS
L22             0 FILE MEDLINE
L23             2 FILE EMBASE
L24             0 FILE USPATFULL

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L26  ANSWER 1 OF 8  CAPLUS  COPYRIGHT 1998 ACS
1998:315984  Document No. 129:49257  Treatment of chronic hepadnavirus
     infection in a woodchuck animal model with an inhibitor of protein
     folding and trafficking.  Block, Timothy M.; Lu, Xuanyong; Mehta,
     Anand S.; Blumberg, Baruch S.; Tennant, Bud; Ebling, Mathew; Korba,
     Brent; Lansky, David M.; Jacob, Gary S.; Dwek, Raymond A. (Viral
     Hepatitis Group, Kimmel Cancer Center, Jefferson Med. Coll.,
     Philadelphia, PA, 19107, USA).  Nat. Med. (N. Y.), 4(5), 610-614
     (English) 1998.  CODEN: NAMEFI.  ISSN: 1078-8956.  Publisher: Nature
     America.
AB   A novel strategy for anti-viral intervention of hepatitis
     B virus (HBV) through the disruption of the proper folding and
     transport of the hepadnavirus glycoproteins is described.  Lab.
     reared woodchucks chronically infected with woodchuck
     hepatitis virus (WHV) were treated with N-nonyl-
     deoxynojirimycin (N-nonyl-DNJ), an inhibitor of the endoplasmic
     reticulum (ER) .alpha.-glucosidases.  The woodchucks experienced
     significant dose dependent decreases in enveloped WHV, resulting in
     undetectable amts. in some cases.  The redn. in viremia correlated
     with the levels of hyperglucosylated glycan in the serum of treated
     animals.  This correlation supports the mechanism of action assocd.
     with the drug and highlights the extreme sensitivity of the virus to
     this type of glycan inhibitor.  At N-nonyl-DNJ concns. that
     prevented WHV secretion, the glycosylation of most serum
     glycoproteins appeared unaffected, suggesting great selectivity for
     this class of therapeutics.  Indeed, this may account for the low
     toxicity of the compd. over the treatment period.  We provide the
     first evidence that glucosidase inhibitors can be used in vivo to
     alter specific steps in the N-linked glycosylation pathway and that
     this inhibition has anti-viral effects.

L26  ANSWER 2 OF 8  EMBASE  COPYRIGHT 1998 ELSEVIER SCI. B.V.
1998174226  EMBASE  The identification and development of antiviral
     agents for the treatment of chronic hepatitis B virus
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infection. Colacino J.M.; Staschke K.A.. J.M. Colacino, Infectious Diseases Research, Lilly Research Laboratories, Indianapolis, IN, United States Minor Outlying Islands. Progress in Drug Research 50/- (259-322) 1998.
Refs: 334.
ISSN: 0071-786X. CODEN: FAZMAE. Pub. Country: Switzerland. Language: English. Summary Language: English.

AB **Hepatitis** B virus (HBV) is the leading cause of chronic **hepatitis** throughout the world. Notwithstanding the availability of a safe and effective vaccine, the world prevalence of HBV has not declined significantly, thus resulting in the need for a selective antiviral agent. HBV is a small, partially double-stranded DNA virus which replicates through an RNA intermediate. Most efforts to develop anti-HBV agents have been targeted to the vital DNA polymerase which possesses reverse transcriptase activity. Currently, the most promising anti-HBV agents are nucleoside analogs which interfere with vital DNA replication. Although earlier nucleoside analogs such as vidarabine (ara-A) and fialuridine (FIAU) have displayed unacceptable toxicities, newer analogs such as lamivudine (3TC), bis-POM PMEA (GS-840), lobucavir, and BMS-200,475 have demonstrated clinical utility. In particular, the use of lamivudine has generated considerable interest in the development of other L-enantiomeric nucleoside analogs for use against HBV. Here, we provide an overview of HBV structure and replication strategy and discuss the use of cell culture systems, in vitro viral polymerase systems, and animal models to identify and evaluate anti- HBV agents. We also discuss the various classes of nucleoside analogs in terms of structure, mechanism of action, status in clinical development, ability to select for resistant HBV variants, and use in combination therapies. Finally, we present a discussion of novel antiviral approaches, including antisense and gene therapy, and address the various challenges to successful anti-HBV chemotherapeutic intervention.

L26 ANSWER 3 OF 8 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
96283202 EMBASE [New drug registrations and licences]. NIEUWE REGISTRATIES EN HANDELSVERGUNNINGEN. Pharmaceutisch Weekblad 131/38 (1070-1071) 1996.
ISSN: 0031-6911. CODEN: PHWEAW. Pub. Country: Netherlands. Language: Dutch.

L26 ANSWER 4 OF 8 CAPLUS COPYRIGHT 1998 ACS
1994:235511 Document No. 120:235511 Secretion of human **hepatitis** B virus is inhibited by the imino sugar N-butyldeoxynojirimycin. Block, Timothy M.; Lu, Xuanyong; Platt, Frances M.; Foster, Graham R.; Gerlich, Wolfram H.; Blumberg, Baruch S.; Dwek, Raymond A. (Jefferson Cancer Inst., Jefferson Med. Coll., Philadelphia, PA, 19107, USA). Proc. Natl. Acad. Sci. U. S. A., 91(6), 2235-9 (English) 1994. CODEN: PNASA6. ISSN: 0027-8424.

AB The imino sugar N-butyldeoxynojirimycin (NBDNJ) is a potent inhibitor of the oligosaccharide-trimming enzyme .alpha.-glucosidase I. **Hepatitis** B virus (HBV) contains three surface proteins (HBs proteins) of different sizes that are singly or doubly N-glycosylated and are essential for the formation of infectious virus. Therefore, the replication and secretion of HBV in the human hepatoma cell line HepG2 were studied in the presence of NBDNJ. In the stably HBV-transfected HepG 2.2.15 cells and in HBV-infected HepG2 cells, NBDNJ suppressed secretion of HBV particles and caused intracellular retention of HBV DNA. The secretion of subviral particles was less affected. These data suggest that inhibitors of oligosaccharide trimming may be useful for antiviral therapy of

hepatitis B and for the study of the intracellular transport of the viral glycoproteins.

L26 ANSWER 5 OF 8 CAPLUS COPYRIGHT 1998 ACS
1994:671340 Document No. 121:271340 N-Butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis. Secretion of human **hepatitis** B virus is inhibited by the imino sugar N-butyldeoxynojirimycin. Ganem, Bruce (Cornell Univ., USA). Chemtracts: Org. Chem., 7(2), 106-7 (English) 1994. CODEN: CMOCEI. ISSN: 0895-4445.
AB N-butyldeoxynojirimycin inhibited the biosynthesis of glycolipids and treated cells infected with **hepatitis** B virus.

L26 ANSWER 6 OF 8 CAPLUS COPYRIGHT 1998 ACS
1994:23538 Document No. 120:23538 Compositions of N-(phosphonoacetyl)-L-aspartic acid and methods of their use as broad spectrum antivirals. Blough, Herbert A. (U.S. Bioscience, Inc., USA). PCT Int. Appl. WO 9318763 A1 930930, 134 pp. DESIGNATED STATES: W: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 93-US2432 930318. PRIORITY: US 92-853454 920318; US 93-32234 930317.
AB Antiviral compns. are described which contain the title compd. and .gtoreq.1 other antiviral agent which act synergistically or additively.

L26 ANSWER 7 OF 8 CAPLUS COPYRIGHT 1998 ACS DUPLICATE 1
1985:592966 Document No. 103:192966 The effects of processing inhibitors of N-linked oligosaccharides on the intracellular migration of glycoprotein E2 of mouse **hepatitis** virus and the maturation of coronavirus particles. Repp, Reinald; Tamura, Teruko; Boschek, C. Bruce; Wege, H.; Schwarz, Ralph T.; Niemann, Heiner (Inst. Med. Virol., Justus-Liebig-Univ., Giessen, D-6300, Fed. Rep. Ger.). J. Biol. Chem., 260(29), 15873-9 (English) 1985. CODEN: JBCHA3. ISSN: 0021-9258.
AB The effects were studied of tunicamycin and inhibitors of the processing of N-linked glycans, including N-methyl-1-deoxynojirimycin, castanospermine, mannodeoxynojirimycin, and swainsonine, on the transport of glycoprotein E2 and the intracellular maturation of the coronavirus mouse **hepatitis** virus A59. Indirect immunofluorescence staining with monoclonal antibodies revealed that glycoprotein E2 exhibits different antigenic properties depending on the presence and the structure of the N-linked oligosaccharides and that efficient transport of glycoprotein E2 to the plasma membrane requires the removal of glucose residues. In the presence of tunicamycin, the nonglycosylated E2 apoprotein was synthesized in normal amts. and readily acylated throughout the infectious cycle. This E2 species could not be detected on the surface of mouse **hepatitis** virus A59-infected cells with indirect immunofluorescence staining or lactoperoxidase labeling. N-Methyl-1-deoxynojirimycin and catanospermine, both of which selectively inhibited the processing glucosidases, caused a drop in virion formation by 2 log steps and a drastic delay in the surface expression of glycoprotein E2. The E2 species synthesized under such conditions was acylated but accumulated intracellularly in a compartment distinct from the Golgi. Concomitantly, synthesis of the matrix glycoprotein E1 of mouse **hepatitis** virus A59 was drastically impaired. Mannodeoxynojirimycin and swainsonine, which block later stages of the processing pathway, had less or no effect on the transport of

glycoprotein E2 and formation of virus particles.

L26 ANSWER 8 OF 8 BIOSIS COPYRIGHT 1998 BIOSIS
85:79605 Document No.: BR28:79605. EFFECTS OF TRIMMING INHIBITORS OF N-LINKED GLYCANS ON THE MATURATION OF MOUSE **HEPATITIS** VIRUS A-59. NIEMANN H; REPP R; TAMURA T; BOSCHEK B; SCHWARZ R T. INST. FUER MED. VIROLOGIE DER UNIV., FRANKFURTER STR. 107, D-6300 GIESSEN. MEETING OF THE GESELLSCHAFT FUER BIOLOGISCHE CHEMIE (SOCIETY FOR BIOLOGICAL CHEMISTRY), GIESSEN, WEST GERMANY, SEPT. 17-20, 1984. HOPPE-SEYLER'S Z PHYSIOL CHEM, 365 (9). 1984. 1040. CODEN: HSZPAZ; ISSN: 0018-4888. Language: English
AN 85:79605 BIOSIS

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DICTIONARY FILE UPDATES: 27 JUL 98 HIGHEST RN 208982-86-9

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Stereochemical name changes have been adopted and appear in CN's beginning 6/29/30. See the online news message for details.

1 72599-27-0/BI
(72599-27-0/RN)
1 151779-14-5/BI
(151779-14-5/RN)
1 69567-10-8/BI
(69567-10-8/RN)
1 81117-35-3/BI
(81117-35-3/RN)
L27 4 (72599-27-0/BI OR 151779-14-5/BI OR 69567-10-8/BI OR 81117-35-3/BI)

=> d 1-4 ide can

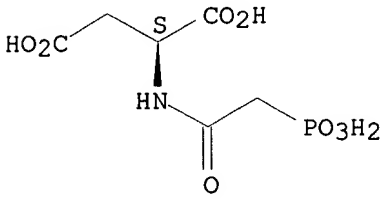
L27 ANSWER 1 OF 4 REGISTRY COPYRIGHT 1998 ACS
RN **151779-14-5** REGISTRY
CN L-Aspartic acid, N-(phosphonoacetyl)-, mixt. with [2R-(2.alpha.,3.beta.,4.alpha.,5.beta.)]-2-(hydroxymethyl)-3,4,5-piperidinetriol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-, [2R-(2.alpha.,3.beta.,4.alpha.,5.beta.)]-, mixt. contg. (9CI)
FS STEREOSEARCH
MF C6 H13 N O4 . C6 H10 N O8 P
CI MXS
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

CM 1

CRN 51321-79-0
CMF C6 H10 N O8 P

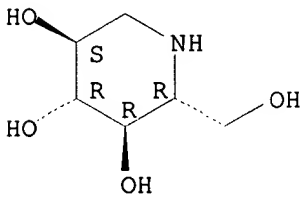
Absolute stereochemistry.



CM 2

CRN 19130-96-2
CMF C6 H13 N O4

Absolute stereochemistry. Rotation (+).

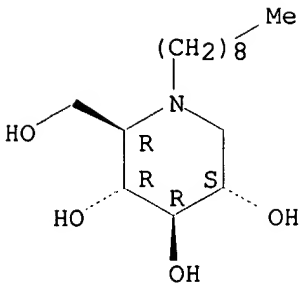


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:23538

L27 ANSWER 2 OF 4 REGISTRY COPYRIGHT 1998 ACS
RN **81117-35-3** REGISTRY
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-nonyl-, [2R-(2.alpha.,3.beta.,4.alpha.,5.beta.)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H31 N O4
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



11 REFERENCES IN FILE CA (1967 TO DATE)
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REFERENCE 1: 129:49257

REFERENCE 2: 124:117885

REFERENCE 3: 124:56564

REFERENCE 4: 122:148109

REFERENCE 5: 122:106392

REFERENCE 6: 117:192258

REFERENCE 7: 115:256562

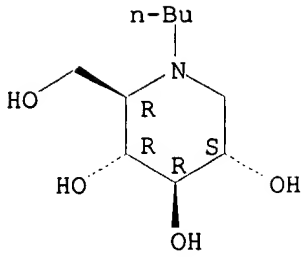
REFERENCE 8: 114:43480

REFERENCE 9: 113:126581

REFERENCE 10: 109:31542

L27 ANSWER 3 OF 4 REGISTRY COPYRIGHT 1998 ACS
RN **72599-27-0** REGISTRY
CN 3,4,5-Piperidinetriol, 1-butyl-2-(hydroxymethyl)-,
[2R-(2.alpha.,3.beta.,4.alpha.,5.beta.)]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN N-Butyl-1-deoxynojirimycin
CN N-Butyldeoxynojirimycin
CN N-Butylmoranoline
CN SC 48334
FS STEREOSEARCH
DR 134282-77-2
MF C10 H21 N O4
CI COM
LC STN Files: ADISINSIGHT, AIDSLINE, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CIN, DRUGNL, DRUGUPDATES, EMBASE, IPA, MEDLINE, NAPRALERT, PNI, PROMT, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



67 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
67 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:16395

REFERENCE 2: 127:341423

REFERENCE 3: 127:341247

REFERENCE 4: 127:214943

REFERENCE 5: 127:181158

REFERENCE 6: 127:146398

REFERENCE 7: 127:16576

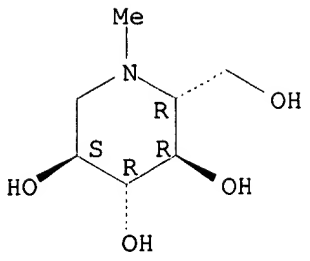
REFERENCE 8: 126:325311

REFERENCE 9: 125:237677

REFERENCE 10: 125:237676

L27 ANSWER 4 OF 4 REGISTRY COPYRIGHT 1998 ACS
RN **69567-10-8** REGISTRY
CN 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-1-methyl-,
[2R-(2.alpha.,3.beta.,4.alpha.,5.beta.)]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN N-Methyl-1-deoxynojirimycin
CN N-Methylmoranolin
CN N-Methylmoranoline
FS STEREOSEARCH
MF C7 H15 N O4
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CSCHEM, EMBASE, IPA, MEDLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



82 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
82 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:8511

REFERENCE 2: 128:171946

REFERENCE 3: 127:181158

REFERENCE 4: 127:16576

REFERENCE 5: 125:276435

REFERENCE 6: 124:278727

REFERENCE 7: 124:249655

REFERENCE 8: 124:106208

REFERENCE 9: 124:56564

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